

BRIEF COMMUNICATION

Anaphylactic bronchospasm during general anesthesia is not related to asthma

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Abstract

In the general population, a history of asthma (HA) is associated with a higher risk of mortality of anaphylactic shock (AS), but it is unknown whether this association remains valid for intra-operative AS. The goal of this retrospective study was to investigate whether a HA was associated with a higher risk of bronchospasm during intra-operative AS. We analyzed 106 patients (January 2009–December 2012) with intra-operative AS: 57% of them had a confirmed IgE-mediated reaction and 27% had a HA. On logistic regression, the only factor statistically associated with bronchospasm was a neuromuscular blocking drug, with both IgE- or non-IgE-mediated reactions. These results suggest that the mechanisms of bronchospasm in AS may be different from those of asthma and that, in the presence of bronchospasm during anesthesia, AS should be considered to be the most likely cause.

As defined by the EAACI, 'anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction' (1). The estimated incidence of anaphylactic shock (AS) during anesthesia is 1/10 000 anesthetic procedures (2). AS can lead to rapid death even in previously healthy individuals (3). According to postmortem studies, death after AS was caused by asphyxia in 50% of cases (pharyngolaryngeal edema, bronchoconstriction) (4). In the general population, asthmatic patients who develop AS are considered to be at higher risk for more severe clinical manifestations and mortality (5). To our knowledge, the relationship between a history of asthma (HA) and clinical manifestations of intra-operative anaphylaxis has not been described. The purpose of this study was to test the hypothesis that a HA modifies the incidence of bronchospasm in patients who develop AS during general anesthesia.

Material and methods

The patients of this cohort are included in the epidemiological studies of the GERAP approved by the Strasbourg Hospitals ethics committee. We retrospectively analyzed

adults with AS during general anesthesia admitted to one single anesthetic allergy reference center for testing from January 2009 to December 2012 [using a standardized diagnostic protocol (6)]. Patients without a detailed report of the reaction were excluded ($n = 32$). Demographic data, HA [according to (7)], atopy [defined as in (1)], allergy [to food, drugs, venom, mites, dust (1)], characteristics of AS severity (8), bronchospasm defined as elevated airway pressures or ventilation difficulties marked in the anesthesia/medical records, treatment and mortality were recorded. IgE-mediated anaphylaxis was diagnosed on the basis of skin tests (9–11) and/or circulating specific IgE (12), otherwise a diagnosis of non-IgE-mediated reaction was adopted. Skin tests were performed for hypnotics, NMBD (suxamethonium, (cis)atracurium, rocuronium), antibiotics, and latex (6).

Comparisons were performed using a t-test and chi-squared test, as appropriate. Logistic regression analyses (bronchospasm as the dependent variable) were performed. A P -value < 0.05 was considered significant. Statistical analyses were performed with R version 3.0.2 software (R foundation for Statistical Computing, Vienna, Austria).

Table 1 Patient characteristics and features of anaphylactic shock

	All patients (<i>n</i> = 106)	HA (<i>n</i> = 29)		No HA (<i>n</i> = 77)	
		IgE-mediated reactions	Non-IgE-mediated reactions	IgE-mediated reactions	Non-IgE-mediated reactions
Age, years	48 ± 15	52 ± 13	45 ± 10	51 ± 15	45 ± 16
Female gender, %	69	93	50	69	66
Atopy, %	36	80*	50	27	22
Time to onset of shock after induction (min)	5 (3; 10)	3 (3; 5)	5 (3; 9)	3 (3; 10)	10 (3; 90)
Bronchospasm, %	33	47	36	42	12
Arterial hypotension, %	58	53	43	73	47
Hypoxemia, %	10	27	7	8	0
Skin symptoms, %	70	67	57	69	78
Causal agent: NMBD, %	43	60	NA	75	NA

NMBD, neuromuscular blocking drugs; HA, History of asthma.

Results are expressed as mean ± SD, median (with interquartile range), or proportions according to the distribution.

**P* < 0.05 asthma vs no asthma in IgE-mediated reactions.

†*P* < 0.05 asthma vs no asthma in non-IgE-mediated reactions (no observations).

Results

Of the 106 patients included, 57% had a confirmed IgE-mediated reaction and 27% had a HA. Bronchospasm occurred as the single manifestation in 3% of AS cases and associated with other signs in 30% of cases. The severity of AS was grade 2 in 50% of cases, grade 1 or 3 in 24% of cases, and grade 4 in 5% of cases. No differences in terms of the grade severity of AS and clinical signs were observed between patients with or without a HA, regardless of the mechanisms considered. Patient characteristics and features of AS are presented in Table 1. A statistically significant association was observed between atopy and a HA on univariate but not on multivariate analysis. The only parameter associated with bronchospasm during AS was NMBD as causal agent (Table 2).

Discussion

In the general population, asthmatic patients experiencing AS are considered to be at higher risk for respiratory mani-

festations (5). However, few data are available concerning the relationship between asthma, bronchospasm, and intra-operative AS (3). The incidences of bronchospasm (2, 11, 13), IgE-, and non-IgE-mediated reactions (14) in this study were similar to those reported in other studies. After logistic regression, NMBD as the causal agent was the only factor statistically associated with bronchospasm. Asthma incidence in our population is higher than in the general French population, which has been reported of 10.2% in 2006 (15). However, our study investigated patients consulting in an allergeo-anesthetic center which may not be representative of the general population.

Autopsy studies of cases of fatal asthma revealed a significantly decreased distribution of lymphatics (16) and increased expression of FcεRI and mast cells in the lungs (17), which at least theoretically suggest an increased risk to mount IgE-mediated and histamine reactions. In the present study, one possible explanation for the lack of association between a HA and bronchospasm during AS could be that in previous study (5) the differences between asthmatic and nonasthmatic patients on the incidence of anaphylaxis and clinical manifestations concerned respiratory signs globally (both the upper and the lower airways), whereas in the present study, the patients being tracheally intubated, we only analyzed the incidence of bronchospasm between patients with vs without a HA. The incidence of respiratory signs was similar in the study of Gonzalez-Perez et al. (5) and in our study (approximately 40%), but they could not differentiate between upper and lower respiratory signs, whereas we only focused on lower respiratory signs.

To our knowledge, the association between bronchospasm and NMBD has been poorly described in previous studies. One explanation for the association observed in this study would be that some NMBD injection leads to mast cell degranulation and release of bronchoconstricting mediators such as histamine and leukotrienes (18). Indeed, injection of antihistamines can abolish some of the bronchoconstrictor

Table 2 Univariate analysis and logistic regression according to the presence of bronchospasm in patients with AS

	Univariate analysis (<i>n</i> = 106)			Logistic regression (<i>n</i> = 106)		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
HA	1.7	0.7; 4	0.26	2.2	0.8; 6	0.1
Causal agent: NMBD	4	1.7; 9.7	0.001	4	1.1; 16.7	0.04
IgE mechanisms	3.1	1.3; 8	0.01	1.2	0.3; 4.6	0.7
Atopy	0.7	0.3; 1.7	0.5			
Causal agent: ATB	0.2	0.01; 1.1	0.1			

CI, confidence interval; NMBD, Neuromuscular Blocking Drug; ATB, antibiotic; HA, History of asthma.

effects of NMBD in rabbits (19). Secondly, NMBD-induced bronchospasm may be related to blockade of M2 muscarinic receptors on prejunctional parasympathetic nerves, leading to vagus nerve-induced bronchospasm (via increased release of acetylcholine, activation of M3 muscarinic receptors and airway smooth muscle constriction) (20). This last pathophysiologic link has been proven for rapacuronium [which has been retrieved from the American market for the major incidence of bronchospasm (21, 22)] and may not be a clinically observable effect of the other NMBD.

One limitation of this study is that it only considered a HA, without providing any more detailed information on severity, as performed by Gonzalez-Perez et al. (5). It was difficult during allergic consultation to have more accurate details of previous asthma episodes. We may hypothesize that bronchial hyper-reactivity may be different in population with active asthma under treatment than with former episodes of asthma. Nevertheless, anesthesiologists consider a HA to be a risk factor for respiratory complications and do not consider all the details of previous asthma to classify the patient's risk. Only considering a previous HA is by consequence of clinical relevance. Although based on only a small sample size, the fact that data were collected by the same physician in a single-center study supports the reliability of these data. Another limitation is that the standardized diagnostic protocol to identify the allergen did not include IgG assays and neutrophil counts, which could be relevant in asthma (6).

Conclusion

These results suggest that a HA may not be related to the development of bronchospasm or the severity of intra-operative AS. We can speculate that asthma and AS are due to different mechanisms of increased airway resistance. This also suggests that bronchospasm occurring during anesthesia should be considered to be due to AS rather than to a HA.

Author contributions

AGC helped to design the study, collected the clinical information, analyzed the raw data, performed statistical analysis, drafted the manuscript, and contributed to the writing of the manuscript. CN conducted all the allergic consultations and helped to design the study. BA helped to design the study and collected the clinical information. PN and SCM performed the biological measurement. PMM, PM, and MA helped to design the study and contributed to the writing of the manuscript. DL helped to design the study, participated with AGC in the interpretation of all data, and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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